

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 April 2000 (12.04.00)
International application No. PCT/US99/18146
International filing date (day/month/year) 10 August 1999 (10.08.99)
Applicant SHALABY, Shalaby, Wahba et al

Applicant's or agent's file reference  
00537/183WO1

Priority date (day/month/year)  
10 August 1998 (10.08.98)

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:  
10 March 2000 (10.03.00)

in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election  was  
 was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>00537/183W01</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/ 18146</b>	International filing date (day/month/year) <b>10/08/1999</b>	(Earliest) Priority Date (day/month/year) <b>10/08/1998</b>
Applicant <b>POLY-MED, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
- 2.  Certain claims were found unsearchable (See Box I).
- 3.  Unity of invention is lacking (see Box II).
- 4. With regard to the title,
  - the text is approved as submitted by the applicant.
  - the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

 None of the figures.

## INTERNATIONAL SEARCH REPORT

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6, 11-16 and 18

Absorbable polyesters having at least one monophosphate functionality per polyester chain, said polyester being able to conjugate with a peptide and/or a bioactive agent which has at least one amino group, wherein the monophosphate functionality forms a linkage with the amino group (N.B. see the definition of absorbable page 6, lines 3-6 of the present description).

2. Claims: 7-10, 17, 26 and 28

Acylated or alkylated absorbable polysaccharides having at least one monophosphate functionality per polyester chain, said polyester being able to conjugate with a peptide and/or a bioactive agent which has at least one amino group, wherein the monophosphate functionality forms a linkage with the amino group.

3. Claim : 20

Method for making a phosphorylated-hydroxyl-bearing polyester which comprises reacting a hydroxyl-bearing polyester with an excess of pyrophosphoric acid.

4. Claim : 23

Method for making phosphorylated microparticles which comprises reacting hydroxyl-bearing microparticles with an excess of pyrophosphoric acid.

5. Claims: 21, 22, 24, 25 and 27

Method for making a phosphorylated -alkylated or -acylated polysaccharide which comprises using pyrophosphoric acid.

6. Claim : 19

Use of an absorbable polyester having at least one monophosphate functionality per polyester chain as an acidic excipient of a cyanoacrylate composition.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/18146

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 C07K7/23 C08G63/91 C08G63/692 C08B37/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K A61L C08G C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 19948 A (ZENECA LTD ; THETFORD DEAN (GB); HOLBROOK MARK (GB)) 5 June 1997 (1997-06-05) comparative example D claim 1; examples 1-8 ---	1,11,12
Y		19,20,27
X	US 5 536 445 A (CAMPBELL FREDERICK ET AL) 16 July 1996 (1996-07-16) paragraph bridging columns 7 and 8 column 2, line 15-38; examples 4,5 ---	1,11
Y		19,20,27
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 June 2000

Date of mailing of the international search report

14.07.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Rousseau, F

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/18146

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R.L.SHOGREN: "Complexes of starch with telechelic poly(e-caprolactone) phosphate" CARBOHYDRATE POLYMERS, vol. 22, 1993, pages 93-98, XP000881303 the whole document	1,11
Y	---	19,20
Y	US 5 672 659 A (MOREAU JACQUES-PIERRE ET AL) 30 September 1997 (1997-09-30) cited in the application the whole document	2,4,5, 13,15, 16,18
Y	---	2,4,5, 13,15, 16,18
Y	US 5 079 337 A (DELLACHERIE EDITH ET AL) 7 January 1992 (1992-01-07)	2,4,5, 13,15, 16,18
Y	claim 1; example 4	8-10,17, 28
Y	---	7
X	DE 44 35 082 C (FRAUNHOFER GES FORSCHUNG) 18 April 1996 (1996-04-18) claim 1	7
X	---	7
X	US 5 310 879 A (TOBIAS PETER S ET AL) 10 May 1994 (1994-05-10) column 2, line 13-16	7
X	---	7
X	EP 0 326 148 A (SUMITOMO CHEMICAL CO ;SUMITOMO PHARMA (JP)) 2 August 1989 (1989-08-02) page 5, line 37-40	7
X	---	7,26
Y	WO 96 31220 A (UNIV PENNSYLVANIA ;JOULLIE MADELEINE (US); WEISZ PAUL B (US); ZHAN) 10 October 1996 (1996-10-10) claims 1,2; figure 4; example 4	8-10,17, 28
Y	page 30, line 3-14	8-10,17, 28
Y	page 31, line 14-16	8-10,17, 28
Y	---	21,22, 24,25,27
Y	US 5 654 422 A (HIRSENKORN ROLF) 5 August 1997 (1997-08-05) column 5, line 3-23; claims 1,8	21,22, 24,25,27
Y	column 3, line 21-23; examples 1,6	21,22, 24,25,27
Y	---	8-10,17, 28
Y	US 4 764 604 A (MUELLER BERND W W) 16 August 1988 (1988-08-16) column 1, line 1-3; claim 1 column 3, line 52-65 column 5, line 18-26	21,22, 24,25
Y	---	21,22, 24,25
	-/-	

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/18146

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 183 809 A (FOLKMAN JUDAH ET AL) 2 February 1993 (1993-02-02) column 6, line 45 -column 7, line 40; claim 1 column 14, line 3-10 ---	8-10,17, 28
Y	EP 0 375 659 A (UNION CARBIDE CORP) 27 June 1990 (1990-06-27) page 5, line 30-32; claim 1 page 6, column 34 -page 7, column 2 ---	19,20
Y	US 5 525 326 A (UNGER EVAN C) 11 June 1996 (1996-06-11) column 4, line 62 -column 5, line 25 column 5, line 32-40 ---	20
Y	GB 1 350 225 A (DIAMOND SHAMROCK CORP) 18 April 1974 (1974-04-18) paragraph bridging pages 2 and 3 page 2, line 24-31 ---	21,22, 24,25,27
Y	EP 0 449 249 A (MITSUI TOATSU CHEMICALS) 2 October 1991 (1991-10-02) page 8, column 34-49 ---	20
Y	EP 0 722 966 A (ETHICON INC) 24 July 1996 (1996-07-24) the whole document ---	20
Y	US 5 635 216 A (THOMPSON WILLIAM W) 3 June 1997 (1997-06-03) the whole document ---	20
Y	US 5 725 881 A (BUCHHOLZ BERTHOLD ET AL) 10 March 1998 (1998-03-10) the whole document ---	20
X	US 4 041 223 A (AMEMIYA KIYOSI ET AL) 9 August 1977 (1977-08-09) column 3, line 37,38; claim 1 ---	23
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1984-210427 '25! XP002140521 & JP 59 122416 A (LION CORP), 14 July 1984 (1984-07-14) abstract ---	23
		-/-

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/18146

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1997-063618 '06! XP002140522 & KR 9 502 607 B (SAMYANG CO LTD) abstract ----	27
Y	EP 0 407 617 A (MITSUI TOATSU CHEMICALS) 16 January 1991 (1991-01-16) page 10, line 4; claims 8,9,11; examples 1-9 page 11, column 24-25 ----	27
Y	GB 2 145 422 A (SANDOZ LTD) 27 March 1985 (1985-03-27) claims 1,14; examples 10-12 ----	27
Y	PATENT ABSTRACTS OF JAPAN vol. 13, no. 95, 6 March 1989 (1989-03-06) & JP 63 273679 A (BIO MATERIAL YUNIBAASU:KK), 10 November 1988 (1988-11-10) abstract ----	19
Y	TSENG YIN CHAO ET AL.: "Effect of poly (D,L-Lactide) addition to 2-cyanoacrylates in their physical properties and toxicity" J. BIOACT. COMPAT. POLYM., vol. 4, no. 2, 1989, pages 101-109, XP000915928 the whole document ----	19
Y	TSENG YIN CHAO: "Medical application of cyanoacrylates as surgical adhesives." JINKO ZOKI , vol. 18, no. 1, 1989, pages 409-413, XP000915929 the whole document ----	19
Y	WO 96 00760 A (TRI POINT MEDICAL LP) 11 January 1996 (1996-01-11) Examples, page 6, lines 15-22 and page 14, lines 21-24 -----	19

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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**INTERNATIONAL SEARCH REPORT**

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PCT/US 99/18146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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**INTERNATIONAL SEARCH REPORT**

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International Application No

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US 5183809 A	02-02-1993	US 5516766 A US 5658894 A US 5760015 A US 5846954 A US 5874419 A US 5935940 A US 5902799 A US 5262404 A		14-05-1996 19-08-1997 02-06-1998 08-12-1998 23-02-1999 10-08-1999 11-05-1999 16-11-1993
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**INTERNATIONAL SEARCH REPORT**

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International Application No

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JP 63273679 A	10-11-1988	JP 7116409 B		13-12-1995

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 99/18146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9600760 A	11-01-1996	AU 690303 B AU 2913095 A BR 9508139 A CA 2193968 A EP 0767819 A JP 10502270 T	23-04-1998 25-01-1996 30-11-1999 11-01-1996 16-04-1997 03-03-1998

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

412+

**PCT**

To  
FISH & RICHARDSON P.C.  
Attn. TSAO, Y.  
225 Franklin Street  
Boston, Massachusetts 02110-2804  
UNITED STATES OF AMERICA

**RECEIVED**

JUL 26 2000

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

FISH & RICHARDSON, P.C.  
BOSTON OFFICE

Date of mailing  
(day month year)

14 07 2000

Applicant's or agent's file reference

00537/183W01

**FOR FURTHER ACTION**

See paragraphs 1 and 4 below

International application No.

PCT/US 99/18146

International filing date

10 08 1999

Applicant

POLY-MED, INC. et al.

1.  The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

REC'D TO RPT  
02/07/2000  
COP 14/00  
02/07/2000

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

U/A

2.  The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  
European Patent Office, P B 5818 Patentlaan 2  
NL-2230 HV Rijswijk  
Tel (+31-70) 340-2040, Tx 31 651 epo nl.  
Fax (+31-70) 340-3016

Authorized officer

Véronique Baillou

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

**When?** Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

**How?** Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**The amendments must be made in the language in which the international application is to be published.**

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

**The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.**

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged,
- (ii) the claim is cancelled,
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed,
- (v) the claim is the result of the division of a claim as filed.

**The following examples illustrate the manner in which amendments must be explained in the accompanying letter:**

1. [Where originally there were 48 claims and after amendment of some claims there are 51].  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11"
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added" or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### **Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

### **Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

REC'D 04 JAN 2001  
WIPO

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference  00537/183WO1	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/US99/18146	International filing date (day/month/year)  10/08/1999	Priority date (day/month/year)  10/08/1998
International Patent Classification (IPC) or national classification and IPC  A61K47/48		
<p>Applicant  POLY-MED, INC. et al.</p> <p style="text-align: right;"><i>5000</i></p>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I     Basis of the report
- II     Priority
- III     Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV     Lack of unity of invention
- V     Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI     Certain documents cited
- VII     Certain defects in the international application
- VIII     Certain observations on the international application

Date of submission of the demand  10/03/2000	Date of completion of this report  28.12.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Rousseau, F  Telephone No. +49 89 2399 8297



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/18146

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

### Description, pages:

1-22 as originally filed

### Claims, No.:

1-28 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,      pages:
- the claims,      Nos.:
- the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/18146

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

## 6. Additional observations, if necessary:

### IV. Lack of unity of invention

#### 1. In response to the invitation to restrict or pay additional fees the applicant has:

- restricted the claims.
- paid additional fees.
- paid additional fees under protest.
- neither restricted nor paid additional fees.

#### 2. This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

#### 3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- complied with.
- not complied with for the following reasons:  
**see separate sheet**

#### 4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- all parts.
- the parts relating to claims Nos. 1-18,26,28.

### V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### 1. Statement

Novelty (N)	Yes:	Claims 2-6,8-10,13-18,28
	No:	Claims 1,7,11,12,26
Inventive step (IS)	Yes:	Claims
	No:	Claims 2-6,8-10,13-18,28
Industrial applicability (IA)	Yes:	Claims 1-18,26,28
	No:	Claims

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

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International application No. PCT/US99/18146

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2. Citations and explanations  
**s separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/18146

**I. Invention (I) :**

1. WO97/19948 (D1) discloses the phosphorylation of polyesters derived from a cyclic lactone (e.g.  $\epsilon$ -caprolactone or  $\gamma$ -valerolactone) using phosphorous pentoxide or polyphosphoric acid as phosphating agent (see examples 1 to 8, claim 1). The polyesters used in examples 1 to 8 of D1 comprise a covalently linked polyethylene glycol segment. D1 also discloses in comparative example C the phosphorylation of poly(12-hydroxystearic acid). Thus, the subject-matter of present claims 1, 11 and 12 lacks novelty in view of D1 (Art. 33(2) PCT).

Phosphorylated polyesters are also disclosed in US-A-5 536 445 (D2), where a poly(hydroxy monocarboxylic acid) is modified with phosphorous pentoxide (see column 2, lines 15-38 and examples 4 and 5). According to the paragraph bridging columns 7 and 8, the preferred polyesters are those derived from hydroxycarboxylic acids or lactones such as 12-hydroxystearic acid and  $\epsilon$ -caprolactone. The subject-matter of present claims 1 and 11 is therefore anticipated by D2 (Art. 33(2) PCT).

The subject-matter of present claims 1 and 11 is also not novel over the article of R.L. Shogren in Carbohydrate Polymers 22 (1993) 93-98 (D3), which also discloses phosphated poly( $\epsilon$ -caprolactone) (Art. 33(2) PCT).

2. Closest prior art for analysis of inventive step of the subject-matter of claims 2-6, 13-16 and 18 is US-A-5 672 659 (D4), which also relates to conjugates of biodegradable polyesters and bioactive polypeptides. The subject-matter of present claims 2-6, 13-16 and 18 differs from D4 in that use is made of monophosphate functionalities instead of carboxylic groups in order to form a linkage with the amino groups of the bioactive polypeptides. In the absence of any evidence for a technical effect arising from the use of monophosphate functionalities instead of carboxylic groups the objective technical problem underlying the present invention is to provide further conjugates of biodegradable polyesters and bioactive polypeptides. The idea of linking the amino groups of a bioactive polypeptide to a polymeric carrier through either phosphate or carboxylate moieties born by the carrier is already known to the skilled person as shown by US-A-5 079 337 (D5) (see claim 1). Hence, if a skilled person starting

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/18146

from D4 wanted to provide further conjugates of biodegradable polyesters and bioactive polypeptides, it would have been obvious for him in view of D5 to try biodegradable polyesters bearing monophosphate functionalities instead of carboxylic groups. Consequently, the subject-matter of present claims 2-6, 13-16 and 18 lacks an inventive step within the meaning of Art. 33(3) PCT.

3. The subject-matter of claims 1-6, 11-16 and 18 is industrially applicable (Art. 33(4) PCT).

**II. Invention (2) :**

1. DE-C-44 35 082 (D6) discloses in claim 1 an acylated cellulose bearing phosphate groups. According to US-A-5 310 879 (D7) (see column 2, lines 13-16) and EP-A-0 326 148 (D8) (see page 5, lines 37-40), Lipid A is a disaccharide esterified with phosphoric and pyrophosphoric acid and also contains ester linked fatty acids, which means that Lipid A fall within the scope of present claim 7. The subject-matter of claim 7 is therefore anticipated by D6, D7 and D8 (Art. 33(2) PCT).

WO96/31220 (D9) discloses in claims 1 and 2 a substituted polyanionic cyclodextrin containing anionic substituents selected from sulfate, nitrate, sulfonate or phosphate and having a hydrophobic substituent selected from the group consisting of alkyl, aryl, ester, ether, thioester and thioether. Compound D as disclosed in Fig. 4 and in example 4 of D9 is an acylated polysaccharide having at least one sulfate group per molecule. Since phosphate groups may be selected as anionic substituents, the compound D as disclosed in D9 but bearing phosphate groups instead of sulfonate groups is therefore disclosed to the skilled reader of D9. Thus, the subject-matter of present claims 7 and 26 lacks novelty over D9 (Art. 33(2) PCT).

2. US-A-5 654 422 (D10), US-A-4 764 604 (D11) and WO96/31220 (D9) represent an equivalent closest state of the art for the analysis of inventive step of the subject-matter of claims 8-10, 17 and 28. D10 discloses in claims 1 and 8 and in column 5, lines 3-23 the use of acylated  $\gamma$ -cyclodextrins for preparing pharmaceutical compositions, in particular for the controlled release of

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/18146

pharmaceutical active compounds. D11 discloses in claim 1, in column 1, lines 1-3, column 3, lines 52-65 and column 5, lines 18-26 the use of  $\gamma$ -cyclodextrin ethers as complexants for pharmaceuticals. The subject-matter of present claims 8-10, 17 and 28 differs from D10 or D11 in that the  $\gamma$ -cyclodextrin bears at least one monophosphate functionality. The cyclodextrins disclosed in D9 are combined with a suitable proteinic growth factor producing an electrostatic complex (see page 30, lines 3-14) and can be of  $\gamma$  type (see page 31, lines 14-16). The subject-matter of present claims 8-10, 17 and 28 differs from D10 or D11 in that a  $\gamma$ -cyclodextrin and a phosphate group have been selected.

The technical problem solved by the use of monophosphate functionalities can be seen as to provide further cyclodextrin compounds for use in pharmaceutical applications. The idea of introducing phosphate functionalities in  $\gamma$ -cyclodextrin polymers in order to bind protein factors is known to the skilled person from US-A-5 183 809 (D12) (see claim 1, passage from column 6, line 45 to column 7, line 40 and column 14, lines 3-10) and from D9. It is pointed that the skilled reader of D12 and D9 understands that the phosphate groups born by the cyclodextrin polymer act as binding sites for the protein factor through ionic bonds. It is also clear for him that in the absence of other reasonable possibilities the parts of the proteins which are ionically anchored to said phosphate groups must be positively charged amine groups. The idea of ionically binding the amino groups of a bioactive polypeptide to a polysaccharide through phosphate moieties born by the polysaccharide is also already known to the skilled person as shown by US-A-5 079 337 (D5) (see claim 1 and example 4). Hence, if a skilled person starting from D10, D11 or D9 wanted to provide further cyclodextrin compounds for use in pharmaceutical applications, it would have been obvious for him in view of D12, D5 and D9 to incorporate monophosphate functionalities in the  $\gamma$ -cyclodextrin polymers. The selection of a  $\gamma$ -cyclodextrin has not been shown to contribute to inventive step either. In the absence of any evidence, that the selection of the specific peptides defined in present claim 10 solves a technical problem in an unexpected manner, one has to conclude that the subject-matter of present claim 10 is an arbitrary rather than a purposive selection and does not involve an inventive step. Consequently, the subject-matter of present claims 8-10, 17 and 28 lacks an inventive step within the meaning of Art. 33(3) PCT.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/18146

3. The subject-matter of claims 7-10, 17, 26 and 28 is industrially applicable (Art. 33(4) PCT).

III. The common concept linking inventions (1) and (2) can be formulated as absorbable polymers having at least one monophosphate functionality, said adsorbable polymer being able to conjugate with a peptide and/or a bioactive agent which has at least one amino group, wherein the monophosphate functionality forms a linkage with the amino group. This concept is already known from D5, which discloses a phosphated dextran, wherein the phosphate group forms an ionic bond with an amino group at an allosteric side on a hemoglobin (see claim 1, example 4, column 6, lines 42-66). Hence, the application does not comply with the requirements of unity of invention (R. 13 PCT).

## ATENT COOPERATION TRADITION

TRG  
YRT  
KAD

From the INTERNATIONAL BUREAU

PCT

**NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

**RECEIVED**

Date of mailing (day/month/year)  
24 February 2000 (24.02.00)

MAR 06 2000

Applicant's or agent's file reference  
~~00537~~/183WO1

**FISH & RICHARDSON, P.C.**

BOSTON OFFICE

**IMPORTANT NOTICE**

International application No.  
PCT/US99/18146

International filing date (day/month/year)  
10 August 1999 (10.08.99)

Priority date (day/month/year)  
10 August 1998 (10.08.98)

Applicant

POLY-MED, INC. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,CN,EP,IL,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,ES,FI,GB,GD,GE,GH,  
GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,  
RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
24 February 2000 (24.02.00) under No. WO 00/09166

**REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)**

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

**REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))**

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Genève 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

Telephone No. (41-22) 338.83.38

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

U.R.T

To:

RECEIVED

TSAO, Y.  
FISH & RICHARDSON P.C.  
225 Franklin Street  
Boston, Massachusetts 02110-2804  
ETATS-UNIS D'AMERIQUE

JAN 03 2001

FISH & RICHARDSON, P.C.  
BOSTON OFFICE

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

28.12.2000

Applicant's or agent's file reference  
00537/183WO1

IMPORTANT NOTIFICATION

International application No.  
PCT/US99/18146

International filing date (day/month/year)  
10/08/1999

Priority date (day/month/year)  
10/08/1998

Applicant

POLY-MED, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

**4. REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Received by PCT Office  
CPT (UOP) 3128101

Initials: UAT

Name and mailing address of the IPEA/

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D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Connolly, M

Tel. +49 89 2399-8021



**PATENT COOPERATION TREATY**  
**PCT**

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 00537/183WO1	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/18146	International filing date (day/month/year) 10/08/1999	Priority date (day/month/year) 10/08/1998	
International Patent Classification (IPC) or national classification and IPC A61K47/48			
Applicant POLY-MED, INC. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I     Basis of the report
- II    Priority
- III    Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV    Lack of unity of invention
- V    Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI    Certain documents cited
- VII    Certain defects in the international application
- VIII    Certain observations on the international application

Date of submission of the demand 10/03/2000	Date of completion of this report 28.12.2000
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Rousseau, F Telephone No. +49 89 2399 8297



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/18146

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).*):

**Description, pages:**

1-22                   as originally filed

**Claims, No.:**

1-28                   as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,       pages:
- the claims,           Nos.:
- the drawings,       sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/18146

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

- restricted the claims.
- paid additional fees.
- paid additional fees under protest.
- neither restricted nor paid additional fees.

2.  This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- complied with.
- not complied with for the following reasons:  
**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- all parts.
- the parts relating to claims Nos. 1-18,26,28.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims 2-6,8-10,13-18,28
	No:	Claims 1,7,11,12,26
Inventive step (IS)	Yes:	Claims
	No:	Claims 2-6,8-10,13-18,28
Industrial applicability (IA)	Yes:	Claims 1-18,26,28
	No:	Claims

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/18146

2. Citations and explanations  
see separate sheet

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/18146

**I. Invention (I) :**

1. WO97/19948 (D1) discloses the phosphorylation of polyesters derived from a cyclic lactone (e.g.  $\epsilon$ -caprolactone or  $\gamma$ -valerolactone) using phosphorous pentoxide or polyphosphoric acid as phosphating agent (see examples 1 to 8, claim 1). The polyesters used in examples 1 to 8 of D1 comprise a covalently linked polyethylene glycol segment. D1 also discloses in comparative example C the phosphorylation of poly(12-hydroxystearic acid). Thus, the subject-matter of present claims 1, 11 and 12 lacks novelty in view of D1 (Art. 33(2) PCT).

Phosphorylated polyesters are also disclosed in US-A-5 536 445 (D2), where a poly(hydroxy monocarboxylic acid) is modified with phosphorous pentoxide (see column 2, lines 15-38 and examples 4 and 5). According to the paragraph bridging columns 7 and 8, the preferred polyesters are those derived from hydroxycarboxylic acids or lactones such as 12-hydroxystearic acid and  $\epsilon$ -caprolactone. The subject-matter of present claims 1 and 11 is therefore anticipated by D2 (Art. 33(2) PCT).

The subject-matter of present claims 1 and 11 is also not novel over the article of R.L. Shogren in Carbohydrate Polymers 22 (1993) 93-98 (D3), which also discloses phosphated poly( $\epsilon$ -caprolactone) (Art. 33(2) PCT).

2. Closest prior art for analysis of inventive step of the subject-matter of claims 2-6, 13-16 and 18 is US-A-5 672 659 (D4), which also relates to conjugates of biodegradable polyesters and bioactive polypeptides. The subject-matter of present claims 2-6, 13-16 and 18 differs from D4 in that use is made of monophosphate functionalities instead of carboxylic groups in order to form a linkage with the amino groups of the bioactive polypeptides. In the absence of any evidence for a technical effect arising from the use of monophosphate functionalities instead of carboxylic groups the objective technical problem underlying the present invention is to provide further conjugates of biodegradable polyesters and bioactive polypeptides. The idea of linking the amino groups of a bioactive polypeptide to a polymeric carrier through either phosphate or carboxylate moieties born by the carrier is already known to the skilled person as shown by US-A-5 079 337 (D5) (see claim 1). Hence, if a skilled person starting

from D4 wanted to provide further conjugates of biodegradable polyesters and bioactive polypeptides, it would have been obvious for him in view of D5 to try biodegradable polyesters bearing monophosphate functionalities instead of carboxylic groups. Consequently, the subject-matter of present claims 2-6, 13-16 and 18 lacks an inventive step within the meaning of Art. 33(3) PCT.

3. The subject-matter of claims 1-6, 11-16 and 18 is industrially applicable (Art. 33(4) PCT).

**II. Invention (2) :**

1. DE-C-44 35 082 (D6) discloses in claim 1 an acylated cellulose bearing phosphate groups. According to US-A-5 310 879 (D7) (see column 2, lines 13-16) and EP-A-0 326 148 (D8) (see page 5, lines 37-40), Lipid A is a disaccharide esterified with phosphoric and pyrophosphoric acid and also contains ester linked fatty acids, which means that Lipid A fall within the scope of present claim 7. The subject-matter of claim 7 is therefore anticipated by D6, D7 and D8 (Art. 33(2) PCT).

WO96/31220 (D9) discloses in claims 1 and 2 a substituted polyanionic cyclodextrin containing anionic substituents selected from sulfate, nitrate, sulfonate or phosphate and having a hydrophobic substituent selected from the group consisting of alkyl, aryl, ester, ether, thioester and thioether. Compound D as disclosed in Fig. 4 and in example 4 of D9 is an acylated polysaccharide having at least one sulfate group per molecule. Since phosphate groups may be selected as anionic substituents, the compound D as disclosed in D9 but bearing phosphate groups instead of sulfonate groups is therefore disclosed to the skilled reader of D9. Thus, the subject-matter of present claims 7 and 26 lacks novelty over D9 (Art. 33(2) PCT).

2. US-A-5 654 422 (D10), US-A-4 764 604 (D11) and WO96/31220 (D9) represent an equivalent closest state of the art for the analysis of inventive step of the subject-matter of claims 8-10, 17 and 28. D10 discloses in claims 1 and 8 and in column 5, lines 3-23 the use of acylated  $\gamma$ -cyclodextrins for preparing pharmaceutical compositions, in particular for the controlled release of

pharmaceutical active compounds. D11 discloses in claim 1, in column 1, lines 1-3, column 3, lines 52-65 and column 5, lines 18-26 the use of  $\gamma$ -cyclodextrin ethers as complexants for pharmaceuticals. The subject-matter of present claims 8-10, 17 and 28 differs from D10 or D11 in that the  $\gamma$ -cyclodextrin bears at least one monophosphate functionality. The cyclodextrins disclosed in D9 are combined with a suitable proteinic growth factor producing an electrostatic complex (see page 30, lines 3-14) and can be of  $\gamma$  type (see page 31, lines 14-16). The subject-matter of present claims 8-10, 17 and 28 differs from D10 or D11 in that a  $\gamma$ -cyclodextrin and a phosphate group have been selected.

The technical problem solved by the use of monophosphate functionalities can be seen as to provide further cyclodextrin compounds for use in pharmaceutical applications. The idea of introducing phosphate functionalities in  $\gamma$ -cyclodextrin polymers in order to bind protein factors is known to the skilled person from US-A-5 183 809 (D12) (see claim 1, passage from column 6, line 45 to column 7, line 40 and column 14, lines 3-10) and from D9. It is pointed that the skilled reader of D12 and D9 understands that the phosphate groups born by the cyclodextrin polymer act as binding sites for the protein factor through ionic bonds. It is also clear for him that in the absence of other reasonable possibilities the parts of the proteins which are ionically anchored to said phosphate groups must be positively charged amine groups. The idea of ionically binding the amino groups of a bioactive polypeptide to a polysaccharide through phosphate moieties born by the polysaccharide is also already known to the skilled person as shown by US-A-5 079 337 (D5) (see claim 1 and example 4). Hence, if a skilled person starting from D10, D11 or D9 wanted to provide further cyclodextrin compounds for use in pharmaceutical applications, it would have been obvious for him in view of D12, D5 and D9 to incorporate monophosphate functionalities in the  $\gamma$ -cyclodextrin polymers. The selection of a  $\gamma$ -cyclodextrin has not been shown to contribute to inventive step either. In the absence of any evidence, that the selection of the specific peptides defined in present claim 10 solves a technical problem in an unexpected manner, one has to conclude that the subject-matter of present claim 10 is an arbitrary rather than a purposive selection and does not involve an inventive step. Consequently, the subject-matter of present claims 8-10, 17 and 28 lacks an inventive step within the meaning of Art. 33(3) PCT.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/18146

3. The subject-matter of claims 7-10, 17, 26 and 28 is industrially applicable (Art. 33(4) PCT).
- III. The common concept linking inventions (1) and (2) can be formulated as absorbable polymers having at least one monophosphate functionality, said adsorbable polymer being able to conjugate with a peptide and/or a bioactive agent which has at least one amino group, wherein the monophosphate functionality forms a linkage with the amino group. This concept is already known from D5, which discloses a phosphated dextran, wherein the phosphate group forms an ionic bond with an amino group at an allosteric side on a hemoglobin (see claim 1, example 4, column 6, lines 42-66). Hence, the application does not comply with the requirements of unity of invention (R. 13 PCT).

**PATENT COOPERATION TREATY**

42+

From the INTERNATIONAL SEARCHING AUTHORITY

**PCT**

To:  
**FISH & RICHARDSON P.C.**  
 Attn. TSAO, Y.  
 225 Franklin Street  
 Boston, Massachusetts 02110-2804  
 UNITED STATES OF AMERICA

**RECEIVED**

JUL 26 2000

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

**FISH & RICHARDSON, P.C.  
BOSTON OFFICE**

Date of mailing  
(day month year)

14.07.2000

Applicant's or agent's file reference

**00537/183W01**

**FOR FURTHER ACTION**

See paragraphs 1 and 4 below

International application No.

**PCT/US 99/ 18146**

International filing date

10.08.1999

Applicant

**POLY-MED, INC. et al.**

1.  The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

REC'D TO RPT  
02T (COP)

9/14/00  
10/14/00

For more detailed instructions, see the notes on the accompanying sheet.

WA

2.  The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL-2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax. (+31-70) 340-3015

Authorized officer

Véronique Baillou

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

**When?** Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

**How?** Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**The amendments must be made in the language in which the international application is to be published.**

#### What documents must/may accompany the amendments?

**Letter (Section 205(b)):**

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

**The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.**

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

**The following examples illustrate the manner in which amendments must be explained in the accompanying letter:**

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### **"Statement under article 19(1)" (Rule 46.4)**

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### **Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

### **Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>00537/183W01</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below	
International application No. <b>PCT/US 99/ 18146</b>	International filing date <b>10 08 1999</b>	(Earliest) Priority Date <b>10 08 1998</b>
Applicant <b>POLY-MED, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **7** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  **Certain claims were found unsearchable** (See Box I).

3.  **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures

# INTERNATIONAL SEARCH REPORT

International application no:  
PCT/US 99/18146

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 5.4(a)

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6, 11-16 and 18

Absorbable polyesters having at least one monophosphate functionality per polyester chain, said polyester being able to conjugate with a peptide and/or a bioactive agent which has at least one amino group, wherein the monophosphate functionality forms a linkage with the amino group (N.B. see the definition of absorbable page 6, lines 3-6 of the present description).

2. Claims: 7-10, 17, 26 and 28

Acylated or alkylated absorbable polysaccharides having at least one monophosphate functionality per polyester chain, said polyester being able to conjugate with a peptide and/or a bioactive agent which has at least one amino group, wherein the monophosphate functionality forms a linkage with the amino group.

3. Claim : 20

Method for making a phosphorylated-hydroxyl-bearing polyester which comprises reacting a hydroxyl-bearing polyester with an excess of pyrophosphoric acid.

4. Claim : 23

Method for making phosphorylated microparticles which comprises reacting hydroxyl-bearing microparticles with an excess of pyrophosphoric acid.

5. Claims: 21, 22, 24, 25 and 27

Method for making a phosphorylated -alkylated or -acylated polysaccharide which comprises using pyrophosphoric acid.

6. Claim : 19

Use of an absorbable polyester having at least one monophosphate functionality per polyester chain as an acidic excipient of a cyanoacrylate composition.

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 C07K7/23 C08G63/91 C08G63/692 C08B37/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K A61L C08G C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 19948 A (ZENECA LTD ; THETFORD DEAN (GB); HOLBROOK MARK (GB)) 5 June 1997 (1997-06-05) comparative example D claim 1; examples 1-8	1,11,12
Y	---	19,20,27
X	US 5 536 445 A (CAMPBELL FREDERICK ET AL) 16 July 1996 (1996-07-16) paragraph bridging columns 7 and 8 column 2, line 15-38; examples 4,5	1,11
Y	---	19,20,27
	-/-	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

27 June 2000

Date of mailing of the international search report

14.07.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Rousseau, F

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	R. L. SHOGREN: "Complexes of starch with telechelic poly( $\epsilon$ -caprolactone) phosphate" CARBOHYDRATE POLYMERS, vol. 22, 1993, pages 93-98, XP000881303 the whole document	1,11
Y	---	19,20
Y	US 5 672 659 A (MOREAU JACQUES-PIERRE ET AL) 30 September 1997 (1997-09-30) cited in the application the whole document	2,4,5, 13,15, 16,18
Y	---	
Y	US 5 079 337 A (DELLACHERIE EDITH ET AL) 7 January 1992 (1992-01-07) claim 1; example 4	2,4,5, 13,15, 16,18
Y	---	8-10,17, 28
X	DE 44 35 082 C (FRAUNHOFER GES FORSCHUNG) 18 April 1996 (1996-04-18) claim 1	7
X	---	
X	US 5 310 879 A (TOBIAS PETER S ET AL) 10 May 1994 (1994-05-10) column 2, line 13-16	7
X	---	
X	EP 0 326 148 A (SUMITOMO CHEMICAL CO ;SUMITOMO PHARMA (JP)) 2 August 1989 (1989-08-02) page 5, line 37-40	7
X	---	
X	WO 96 31220 A (UNIV PENNSYLVANIA ;JOULLIE MADELEINE (US); WEISZ PAUL B (US); ZHAN) 10 October 1996 (1996-10-10) claims 1,2; figure 4; example 4	7,26
Y	page 30, line 3-14	8-10,17, 28
	page 31, line 14-16	
Y	---	
Y	US 5 654 422 A (HIRSENKORN ROLF) 5 August 1997 (1997-08-05) column 5, line 3-23; claims 1,8	8-10,17, 28
Y	column 3, line 21-23; examples 1,6	21,22, 24,25,27
Y	---	
Y	US 4 764 604 A (MUELLER BERND W W) 16 August 1988 (1988-08-16) column 1, line 1-3; claim 1 column 3, line 52-65 column 5, line 18-26	8-10,17, 28
Y	---	21,22, 24,25

-/-

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	US 5 183 809 A (FOLKMAN JUDAH ET AL) 2 February 1993 (1993-02-02) column 6, line 45 -column 7, line 40; claim 1 column 14, line 3-10 ---	8-10,17, 28
Y	EP 0 375 659 A (UNION CARBIDE CORP) 27 June 1990 (1990-06-27) page 5, line 30-32; claim 1 page 6, column 34 -page 7, column 2 ---	19,20
Y	US 5 525 326 A (UNGER EVAN C) 11 June 1996 (1996-06-11) column 4, line 62 -column 5, line 25 column 5, line 32-40	20
Y	---	21,22, 24,25,27
Y	GB 1 350 225 A (DIAMOND SHAMROCK CORP) 18 April 1974 (1974-04-18) paragraph bridging pages 2 and 3 page 2, line 24-31 ---	20
Y	EP 0 449 249 A (MITSUI TOATSU CHEMICALS) 2 October 1991 (1991-10-02) page 8, column 34-49 ---	20
Y	EP 0 722 966 A (ETHICON INC) 24 July 1996 (1996-07-24) the whole document ---	20
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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 99/18146

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9600760	A 11-01-1996	AU	690303 B	23-04-1998
		AU	2913095 A	25-01-1996
		BR	9508139 A	30-11-1999
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## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference  00537/183WO1	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/US99/18146	International filing date (day/month/year)  10/08/1999	Priority date (day/month/year)  10/08/1998	
International Patent Classification (IPC) or national classification and IPC A61K47/48			
Applicant  POLY-MED, INC. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I     Basis of the report
- II    Priority
- III    Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV    Lack of unity of invention
- V    Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI    Certain documents cited
- VII    Certain defects in the international application
- VIII    Certain observations on the international application

Date of submission of the demand  10/03/2000	Date of completion of this report  28.12.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 1426	Authorized officer  Rousseau, F



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/18146

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*):

Description, pages:

1-22 as originally filed

Claims, No.:

1-28 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,      pages:
- the claims,      Nos.:
- the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

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*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

- restricted the claims.
- paid additional fees.
- paid additional fees under protest.
- neither restricted nor paid additional fees.

2.  This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- complied with.
- not complied with for the following reasons:  
*see separate sheet*

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- all parts.
- the parts relating to claims Nos. 1-18,26,28.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims 2-6,8-10,13-18,28
	No:	Claims 1,7,11,12,26
Inventive step (IS)	Yes:	Claims
	No:	Claims 2-6,8-10,13-18,28
Industrial applicability (IA)	Yes:	Claims 1-18,26,28
	No:	Claims

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2. Citations and explanations  
see separate sheet

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EXAMINATION REPORT - SEPARATE SHEET**

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**I. Invention (I) :**

1. WO97/19948 (D1) discloses the phosphorylation of polyesters derived from a cyclic lactone (e.g.  $\epsilon$ -caprolactone or  $\gamma$ -valerolactone) using phosphorous pentoxide or polyphosphoric acid as phosphating agent (see examples 1 to 8, claim 1). The polyesters used in examples 1 to 8 of D1 comprise a covalently linked polyethylene glycol segment. D1 also discloses in comparative example C the phosphorylation of poly(12-hydroxystearic acid). Thus, the subject-matter of present claims 1, 11 and 12 lacks novelty in view of D1 (Art. 33(2) PCT).

Phosphorylated polyesters are also disclosed in US-A-5 536 445 (D2), where a poly(hydroxy monocarboxylic acid) is modified with phosphorous pentoxide (see column 2, lines 15-38 and examples 4 and 5). According to the paragraph bridging columns 7 and 8, the preferred polyesters are those derived from hydroxycarboxylic acids or lactones such as 12-hydroxystearic acid and  $\epsilon$ -caprolactone. The subject-matter of present claims 1 and 11 is therefore anticipated by D2 (Art. 33(2) PCT).

The subject-matter of present claims 1 and 11 is also not novel over the article of R.L. Shogren in Carbohydrate Polymers 22 (1993) 93-98 (D3), which also discloses phosphated poly( $\epsilon$ -caprolactone) (Art. 33(2) PCT).

2. Closest prior art for analysis of inventive step of the subject-matter of claims 2-6, 13-16 and 18 is US-A-5 672 659 (D4), which also relates to conjugates of biodegradable polyesters and bioactive polypeptides. The subject-matter of present claims 2-6, 13-16 and 18 differs from D4 in that use is made of monophosphate functionalities instead of carboxylic groups in order to form a linkage with the amino groups of the bioactive polypeptides. In the absence of any evidence for a technical effect arising from the use of monophosphate functionalities instead of carboxylic groups the objective technical problem underlying the present invention is to provide further conjugates of biodegradable polyesters and bioactive polypeptides. The idea of linking the amino groups of a bioactive polypeptide to a polymeric carrier through either phosphate or carboxylate moieties born by the carrier is already known to the skilled person as shown by US-A-5 079 337 (D5) (see claim 1). Hence, if a skilled person starting

from D4 wanted to provide further conjugates of biodegradable polyesters and bioactive polypeptides, it would have been obvious for him in view of D5 to try biodegradable polyesters bearing monophosphate functionalities instead of carboxylic groups. Consequently, the subject-matter of present claims 2-6, 13-16 and 18 lacks an inventive step within the meaning of Art. 33(3) PCT.

3. The subject-matter of claims 1-6, 11-16 and 18 is industrially applicable (Art. 33(4) PCT).

**II. Invention (2) :**

1. DE-C-44 35 082 (D6) discloses in claim 1 an acylated cellulose bearing phosphate groups. According to US-A-5 310 879 (D7) (see column 2, lines 13-16) and EP-A-0 326 148 (D8) (see page 5, lines 37-40), Lipid A is a disaccharide esterified with phosphoric and pyrophosphoric acid and also contains ester linked fatty acids, which means that Lipid A fall within the scope of present claim 7. The subject-matter of claim 7 is therefore anticipated by D6, D7 and D8 (Art. 33(2) PCT).

WO96/31220 (D9) discloses in claims 1 and 2 a substituted polyanionic cyclodextrin containing anionic substituents selected from sulfate, nitrate, sulfonate or phosphate and having a hydrophobic substituent selected from the group consisting of alkyl, aryl, ester, ether, thioester and thioether. Compound D as disclosed in Fig. 4 and in example 4 of D9 is an acylated polysaccharide having at least one sulfate group per molecule. Since phosphate groups may be selected as anionic substituents, the compound D as disclosed in D9 but bearing phosphate groups instead of sulfonate groups is therefore disclosed to the skilled reader of D9. Thus, the subject-matter of present claims 7 and 26 lacks novelty over D9 (Art. 33(2) PCT).

2. US-A-5 654 422 (D10), US-A-4 764 604 (D11) and WO96/31220 (D9) represent an equivalent closest state of the art for the analysis of inventive step of the subject-matter of claims 8-10, 17 and 28. D10 discloses in claims 1 and 8 and in column 5, lines 3-23 the use of acylated  $\gamma$ -cyclodextrins for preparing pharmaceutical compositions, in particular for the controlled release of

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pharmaceutical active compounds. D11 discloses in claim 1, in column 1, lines 1-3, column 3, lines 52-65 and column 5, lines 18-26 the use of  $\gamma$ -cyclodextrin ethers as complexants for pharmaceuticals. The subject-matter of present claims 8-10, 17 and 28 differs from D10 or D11 in that the  $\gamma$ -cyclodextrin bears at least one monophosphate functionality. The cyclodextrins disclosed in D9 are combined with a suitable proteinic growth factor producing an electrostatic complex (see page 30, lines 3-14) and can be of  $\gamma$  type (see page 31, lines 14-16). The subject-matter of present claims 8-10, 17 and 28 differs from D10 or D11 in that a  $\gamma$ -cyclodextrin and a phosphate group have been selected.

The technical problem solved by the use of monophosphate functionalities can be seen as to provide further cyclodextrin compounds for use in pharmaceutical applications. The idea of introducing phosphate functionalities in  $\gamma$ -cyclodextrin polymers in order to bind protein factors is known to the skilled person from US-A-5 183 809 (D12) (see claim 1, passage from column 6, line 45 to column 7, line 40 and column 14, lines 3-10) and from D9. It is pointed that the skilled reader of D12 and D9 understands that the phosphate groups born by the cyclodextrin polymer act as binding sites for the protein factor through ionic bonds. It is also clear for him that in the absence of other reasonable possibilities the parts of the proteins which are ionically anchored to said phosphate groups must be positively charged amine groups. The idea of ionically binding the amino groups of a bioactive polypeptide to a polysaccharide through phosphate moieties born by the polysaccharide is also already known to the skilled person as shown by US-A-5 079 337 (D5) (see claim 1 and example 4). Hence, if a skilled person starting from D10, D11 or D9 wanted to provide further cyclodextrin compounds for use in pharmaceutical applications, it would have been obvious for him in view of D12, D5 and D9 to incorporate monophosphate functionalities in the  $\gamma$ -cyclodextrin polymers. The selection of a  $\gamma$ -cyclodextrin has not been shown to contribute to inventive step either. In the absence of any evidence, that the selection of the specific peptides defined in present claim 10 solves a technical problem in an unexpected manner, one has to conclude that the subject-matter of present claim 10 is an arbitrary rather than a purposive selection and does not involve an inventive step. Consequently, the subject-matter of present claims 8-10, 17 and 28 lacks an inventive step within the meaning of Art. 33(3) PCT.

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3. The subject-matter of claims 7-10, 17, 26 and 28 is industrially applicable (Art. 33(4) PCT).
- III. The common concept linking inventions (1) and (2) can be formulated as absorbable polymers having at least one monophosphate functionality, said adsorbable polymer being able to conjugate with a peptide and/or a bioactive agent which has at least one amino group, wherein the monophosphate functionality forms a linkage with the amino group. This concept is already known from D5, which discloses a phosphated dextran, wherein the phosphate group forms an ionic bond with an amino group at an allosteric side on a hemoglobin (see claim 1, example 4, column 6, lines 42-66). Hence, the application does not comply with the requirements of unity of invention (R. 13 PCT).